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0225042.1 28 October 2002 (28.10.2002) GB

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

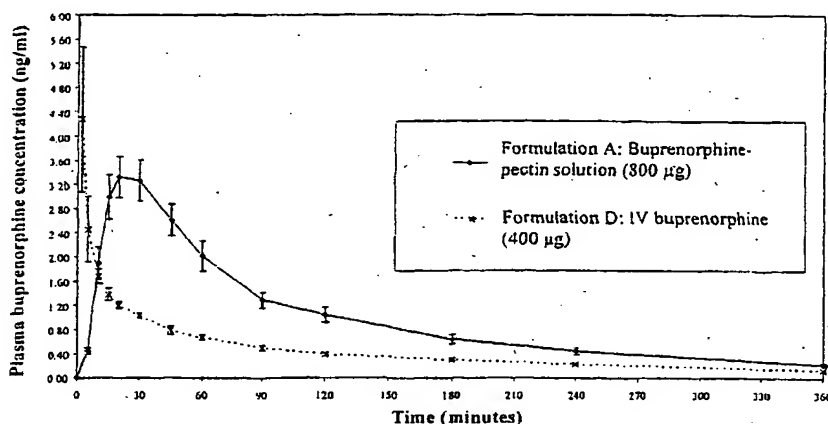
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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[Continued on next page]

(54) Title: **FORMULATION**



(57) **Abstract:** Aqueous formulations suitable for intranasal administration comprise buprenorphine or a physiologically acceptable salt or ester thereof and (a) a pectin having a degree of esterification of less than 50%, (b) chitosan and a polyoxyethylene-polyoxypropylene copolymer (poloxamer) or (c) chitosan and hydroxypropylmethylcellulose. Such formulations can induce rapid and prolonged analgesia when delivered intranasally to a patient. The buprenorphine or buprenorphine salt or ester may be delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration of buprenorphine, C_{ther} , of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours.



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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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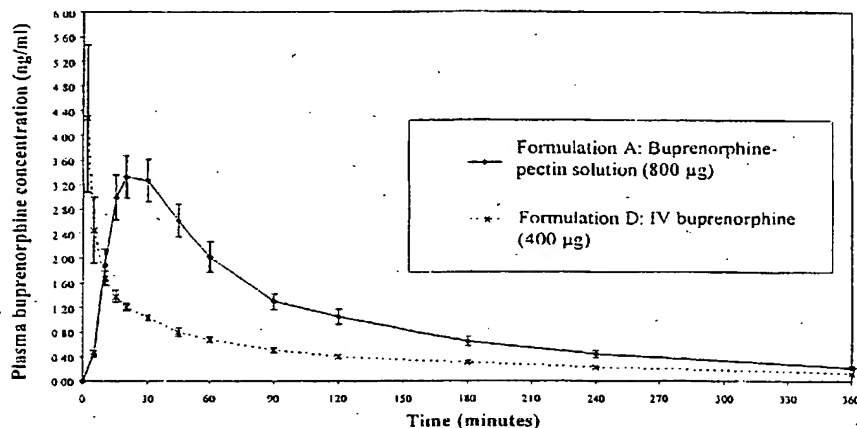
(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: FORMULATION COMPRISING BUPRENORPHINE



(57) Abstract: Aqueous formulations suitable for intranasal administration comprise buprenorphine or a physiologically acceptable salt or ester thereof and (a) a pectin having a degree of esterification of less than 50%, (b) chitosan and a polyoxyethylene-polyoxypropylene copolymer (poloxamer) or (c) chitosan and hydroxypropylmethylcellulose. Such formulations can induce rapid and prolonged analgesia when delivered intranasally to a patient. The buprenorphine or buprenorphine salt or ester may be delivered to the bloodstream to produce within 30 minutes a therapeutic plasma concentration of buprenorphine, C_{ther} , of 0.2 ng/ml or greater which is maintained for a duration T_{maint} of at least 2 hours.



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 03/01183

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 41-49 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15,44 completely, 38-43,45-50 partially

An aqueous solution suitable for intranasal administration of buprenorphine, comprising pectin having a degree of esterification of less than 50 %.

2. Claims: 16-18,35 completely, 23-34,37-43,45-50 partially

An aqueous solution suitable for intranasal administration of buprenorphine, comprising chitosan and hydroxypropylmethylcellulose.

3. Claims: 19-22,36 completely, 23-34,37-43,45-50 partially

An aqueous solution suitable for intranasal administration of buprenorphine, comprising chitosan and polyoxyethylene-polyoxypropylene.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/01183

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/36 A61K31/485 A61K9/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 11, 3 January 2001 (2001-01-03) & JP 2000 229859 A (TEIJIN LTD), 22 August 2000 (2000-08-22) abstract	1-15, 38-50
Y	---	16-18, 23-35, 37-50
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 September 2003

Date of mailing of the international search report

17. 10. 2003

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VON EGGEKRAUT, S

INTERNATIONAL SEARCH REPORT

onal Application No

PCI/GB 03/01183

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 47535 A (WATTS PETER JAMES ;DANBIOSYST UK (GB); ILLUM LISBETH (GB)) 29 October 1998 (1998-10-29) cited in the application page 2, last paragraph page 5, paragraph 2 page 9, last paragraph page 11, paragraph 3 page 16, line 28 -page 17, line 3 example 1	1-15, 38-50
A	WO 99 27905 A (WATTS PETER JAMES ;DANBIOSYST UK (GB); ILLUM LISBETH (GB)) 10 June 1999 (1999-06-10) page 12, paragraph 4 page 13, paragraph 3 page 15, paragraph 1 example 1	1-15, 38-50
A	WO 93 15737 A (DANBIOSYST UK) 19 August 1993 (1993-08-19) page 1, paragraph 1 page 3, line 19 example 5	1-15, 38-50
A	WO 01 29046 A (WEST PHARM SERV DRUG RES LTD) 26 April 2001 (2001-04-26) page 1, paragraph 1 page 4, line 12 page 5, line 1 - line 18 example 2	1-15, 38-50
A	WO 99 09962 A (RECKITT&COLMAN) 4 March 1999 (1999-03-04) examples 1,10,12	1-15, 38-50
P,A	WO 02 067897 A (CARRINGTON LAB INC) 6 September 2002 (2002-09-06) example 4	1-15, 38-50
Y	EP 0 571 671 A (PROCTER & GAMBLE) 1 December 1993 (1993-12-01) examples 1,2 page 2, line 38 - line 44 page 2, line 53 -page 3, line 6	16-18, 23-35, 37-50
X	WO 02 00195 A (EPICEPT CORP) 3 January 2002 (2002-01-03) page 3, line 3 - line 14 page 7, line 10 examples 1,2	19-34, 36-43, 45-50

INTERNATIONAL SEARCH REPORT

Inventor's Application No

PC 1/GB 03/01183

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 2000229859	A	22-08-2000	NONE	
WO 9847535	A	29-10-1998	AU 741847 B2	13-12-2001
			AU 7064798 A	13-11-1998
			EP 0975367 A1	02-02-2000
			WO 9847535 A1	29-10-1998
			GB 2340039 A , B	16-02-2000
			JP 2001524094 T	27-11-2001
			NO 995021 A	15-10-1999
			NZ 337289 A	29-06-2001
			US 2002197324 A1	26-12-2002
			US 6432440 B1	13-08-2002
			ZA 9803262 A	18-10-1999
WO 9927905	A	10-06-1999	AU 751182 B2	08-08-2002
			AU 1253599 A	16-06-1999
			CA 2312839 A1	10-06-1999
			EP 1035833 A1	20-09-2000
			WO 9927905 A1	10-06-1999
			JP 2001524509 T	04-12-2001
			NO 20002851 A	02-06-2000
			US 6342251 B1	29-01-2002
			US 2001046519 A1	29-11-2001
			ZA 9810886 A	29-05-2000
WO 9315737	A	19-08-1993	AT 171872 T	15-10-1998
			AU 3458093 A	03-09-1993
			CA 2127805 A1	19-08-1993
			DE 69321458 D1	12-11-1998
			DE 69321458 T2	18-03-1999
			DK 625044 T3	21-06-1999
			EP 0625044 A1	23-11-1994
			ES 2123660 T3	16-01-1999
			WO 9315737 A1	19-08-1993
			GB 2277682 A , B	09-11-1994
			JP 7503481 T	13-04-1995
			NO 942787 A	27-07-1994
			US 5629011 A	13-05-1997
WO 0129046	A	26-04-2001	AU 7933500 A	30-04-2001
			CA 2388395 A1	26-04-2001
			EP 1224188 A2	24-07-2002
			WO 0129046 A2	26-04-2001
			JP 2003512380 T	02-04-2003
			NO 20021815 A	14-06-2002
			US 6387917 B1	14-05-2002
WO 9909962	A	04-03-1999	AT 244562 T	15-07-2003
			AU 737714 B2	30-08-2001
			AU 8738998 A	16-03-1999
			BR 9811245 A	18-07-2000
			CA 2301165 A1	04-03-1999
			CN 1267216 T	20-09-2000
			DE 69816307 D1	14-08-2003
			EP 1007015 A1	14-06-2000
			WO 9909962 A1	04-03-1999
			GB 2328443 A , B	24-02-1999
			HU 0003602 A2	28-03-2001

Continuation of Box I.2

Present claims

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Int. Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9909962	A		JP 2001513549 T PL 338701 A1 US 6391294 B1 ZA 9807516 A	04-09-2001 20-11-2000 21-05-2002 22-02-1999
WO 02067897	A	06-09-2002	US 2002119941 A1 WO 02067897 A2	29-08-2002 06-09-2002
EP 0571671	A	01-12-1993	EP 0571671 A1 AT 158172 T AU 669902 B2 AU 4223493 A CA 2136607 A1 DE 69222295 D1 DE 69222295 T2 JP 7507303 T WO 9324149 A1	01-12-1993 15-10-1997 27-06-1996 30-12-1993 09-12-1993 23-10-1997 09-04-1998 10-08-1995 09-12-1993
WO 0200195	A	03-01-2002	AU 7017701 A CA 2413545 A1 EP 1296650 A2 WO 0200195 A2 US 2002192288 A1 US 2003124190 A1 US 2002013331 A1	08-01-2002 03-01-2002 02-04-2003 03-01-2002 19-12-2002 03-07-2003 31-01-2002

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